

TITLE: Secular trends in the incidence and prevalence of gout in Denmark from 1995-2015: A Nationwide Register-based study.

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ABSTRACT

Objectives: To investigate temporal trends in the incidence and prevalence of gout in the adult Danish population.

Methods: Using the nationwide Danish National Patient Registry, we calculated the number of incident gout patients (per 100,000 person-years) within each 1-year period from 1995 to 2015, and the prevalence of gout in 2000 and 2015. Further, we calculated age- and gender-specific incidence rates of gout from 1995 to 2015.

Results: We identified a total of 45,685 incident gout patients (72.9% males) with a mean (SD) age of 65 (16) years at diagnosis. In both genders an increase in age-standardised incidence rates was observed from 32.3/100,000 [95%CI 30.7 to 33.9] in 1995 to 57.5/100,000 [95%CI 55.6 to 59.5] in 2015 ($p < 0.001$). Similar trends were observed for 8,950 cases diagnosed at rheumatology departments. We likewise observed an increase in the prevalence of gout from 0.29% [95%CI 0.29 to 0.30] in 2000 to 0.68% [95%CI 0.68 to 0.69] in 2015.

Conclusions: The annual incidence rate of gout increased by almost 80% in Denmark between 1995 and 2015. The prevalence increased by nearly 130% between 2000 and 2015. Reasons for this are unknown but may include an increase in risk factors e.g. obesity, diabetes mellitus, longer life expectancy and increased awareness of the disease amongst patients and/or health professionals.

INTRODUCTION:

Gout is the most prevalent chronic inflammatory arthritis in the Western world. It is characterized by deposits of monosodium urate crystal in joints and other tissues, resulting in severe joint inflammation in some patients. Great regional and ethnical variations in prevalence have been reported, ranging from 0.9% in France to 3.9% in the US and a stunning 10% in the male Maori population in New Zealand.[1]

The prevalence of gout is expected to increase in the coming years as a consequence of the increasing prevalence of established risk factors for gout, e.g. diabetes mellitus, hypertension, metabolic syndrome, cardiovascular disease, kidney disease and an aging population. Studies on the secular trends in incidence and prevalence of gout are scarce, mostly because of limited periods of data coverage in most electronic databases. Existing studies are few, and those from Scandinavia have been limited to certain regions within a country.[2–4]

Given the universal, tax-funded, and long-term existence of a national healthcare system and registers, routinely collected Danish health care data offer a unique opportunity for epidemiological research. We took advantage of the existence of the Danish health registries to examine the incidence, prevalence and secular trends of gout, in a nationwide cohort covering the last two decades.

MATERIAL AND METHODS:

Study design: Population-based, nationwide, register-based study examining the incidence and prevalence of gout in Denmark from 1995-2015. The study methods and results are reported according to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement.[5]

Data sources: We used the unique Civil Personal Registration (CPR) number assigned to all Danish residents, to link the Civil Registration System (CRS) and the Danish National Patient Register (DNPR).

CRS: a virtually complete register of all persons born in Denmark or residing legally in the country for more than 3 months. CRS contains updated information on sex, date of birth, vital- and emigration status and dates.[6]

DNPR: a register where all inpatient hospital contacts are registered since 1977. Outpatient hospital contacts have been registered since 1995. DNPR includes information on 1 primary and up to 19 secondary discharge diagnoses per patient contact. Diagnostic coding is carried out in accordance with the International Classification of Diseases (ICD) using the 8th revision (ICD-8) between 1978 and 1994 and the 10th revision (ICD-10) from 1994 and onwards.[7]

Study population: Incident gout patients aged ≥ 18 years were defined as patients with a first ever recorded diagnosis of gout (ICD-10:M10 and M14.0) in DNPR between 1/1/1995 and 31/12/2015. We excluded prevalent gout patients with a first diagnosis (ICD-8: 274) recorded between 1977 and 1994. In the prevalence calculations, we used DNPR data going back to 1977.

Statistical Analysis: To estimate secular trends in incidence of gout, we calculated the annual incidence rate of gout as the number of newly diagnosed gout cases divided by the underlying Danish population at risk in each given calendar year. The underlying population ~~are~~is available from Statistics Denmark. Incidence rates were then age-standardized according to the NORDCAN standard population.[8] Additionally, age and sex-specific incidence rates were calculated by stratifying both numerator and denominator into sex and age (5-year) bands. Using the Poisson distribution, we calculated 95% confidence intervals (95%CI), and calculated the average increase in incidence rate per year using a Poisson log-linear model with the logarithm of person years as offset. All of the above calculations were then carried out for gout patients diagnosed at a rheumatology department, in an attempt to identify more severe cases.

Including cases going back to 1977, the point prevalence of gout among all adults in Denmark was estimated with the denominator being all Danes alive and living in Denmark at 31/12/2000 and at 31/12/2015. Prevalence was reported for the total population, gender specific and within age-groups (18-29, 30-39, 40-49, 50-59, 60-69, 70-79, 80+ years). We estimated 95% confidence intervals using the Wilson method.

R (version 3.2.5) was used for all statistical analysis (base R and packages: dplyr, lubridate, popEpi, survival).

Ethics: Approval from the ethics committee is not required for registry-based research in Denmark. Study approval was obtained from the Danish data protection agency (j.nr.: 2012-58-0004).

RESULTS:

During the 20-year study period (1995-2015) we identified 45,685 incident cases of gout of which 8,950 (19.6% of total) had their first diagnosis at a rheumatology department (Supplementary Figure 1). There was a male predominance (72.9%) and the mean overall age at diagnosis was 65.3 ± 16.2 years. Males were younger at time of diagnosis (63.0 ± 15.7 years) compared to females (71.4 ± 15.9 years).

Age-standardized incidence rates (per 100,000 person-years) across the study period are depicted in Figure 1, and a 1.8-fold increase in overall incidence is seen: from 32.3/100,000 [95%CI 30.7 to 33.9] in 1995 to 57.5/100,000 [95%CI 55.6 to 59.6] person-years in 2015 ($p < 0.001$). In the Poisson model this corresponded to an annual increase of 1.03 cases / 100,000 person-years, although this is likely an underestimate. We found a steeper increase in incidence from 2008 to 2015.

Similar trends, but with lower incidence rates were observed when restricting our analysis to gout patients diagnosed at a rheumatology department. The age- and sex specific incidence rates increased progressively with increasing age for both sexes, most markedly in patients aged 60 years and above (Supplementary Figure 2).

We found a 2.3-fold increase in overall prevalence from 2000 to 2015, as we identified 11,734 patients with gout in 2000 resulting in a prevalence of 0.29% [95%CI 0.288 to 0.299] in an underlying adult population of 3,996,930. In 2015 we identified 28,306 patients resulting in a prevalence of 0.68% [95%CI 0.677 to 0.692] in an underlying population of 4,153,680. The within age-subgroup specific prevalence increased progressively in elder age-groups, reaching 1.99% among the 80+ year olds. Looking at the gender specific prevalence rates we observed similar results. Notably we found that among males the prevalence rates increased markedly among the 40-49 year old's whereas a similar increase in prevalence was seen among females in the 60-69 year old's (Figure 2).

DISCUSSION

In this nationwide register-based cohort study we found a 1.8-fold increase in the incidence rate of gout in Denmark from 1995 to 2015 and a 2.3-fold increase in prevalence from 2000 to 2015. We found an incidence rate of 57.5/100,000-person years and a prevalence of 0.68% of gout in the Danish population in 2015.

The reported incidence rates of gout in other countries have varied considerably – e.g. Trifero et al. reported an incidence of 95/100,000 person-years in the adult Italian population in the period 2005-2009,[9] whereas Cea Soriano et al. reported an incidence of 268/100,000 person-years in a UK population in the period 2000-2007.[10] These varying incidence rates probably reflect a high degree of heterogeneity in the study populations regarding age, sex, race as well as the registration procedures in the country-specific health care systems. By including data spanning two decades on patients of both sexes and all age groups, the current study is, to our knowledge, the largest to investigate secular incidence rates in gout. There was a distinct increase in incidence from 2008 to 2015. This could reflect a real increase in incidence of gout or a change in diagnostic coding / treatment practice. Of the latter, one such possibility could be the introduction of new guidelines, e.g. the 2006 EULAR management guidelines and the 2007 national treatment guidelines for gout from The Danish Society for Rheumatology.[11,12] Like incidence rates, different prevalence rates of gout have been reported throughout the world, and even among developed countries in Europe the estimated prevalence ranges from 0.3% in Portugal to 4.75% in Greece.[13,14] As with incidence, prevalence estimates of gout may vary between studies due to differences in case definition and sampling methods, calendar periods studied, age and sex distribution.

Overall incidence and prevalence rates increase with age for both sexes. Notably we find that the incidence and prevalence among females is very low before menopausal age but rapidly increase in older age-groups to about half of that observed in males. Similar findings are reported by others,[15] and it has been speculated that the uricosuric action of oestrogen accounts for the lower incidence among premenopausal women.[16]

Our study is based on a nationwide data covering all in- and outpatients from all Danish hospitals, which strengthens the external validity of the results. However, some limitations need to be considered. First, DNPR only records data from hospital records (both in- and outpatient) and ~~some-a few~~ private practices whereas milder cases of gout managed in primary care are not registered. Thus, the true rates of gout in the ~~total~~ Danish population are most likely higher than those reported in the present study here. Second, the diagnosis of gout has not been validated in the DNPR. However, it has previously been reported that within the DNPR, there is generally a high validity of the included diagnosis, for instance the connective tissue diagnoses used for calculation of the Charlson Comorbidity Index have been found to have a positive predictive value of 98%.[17] The year 2000 was

chosen as the first year to estimate prevalence as the DNPR first started recording outpatient data in the year 1995 and time to include cases before 1995 was needed. Nonetheless the prevalence estimate for 2000 may still be low due to gout patients treated in outpatient clinics before 1995 not being registered in DNPR.

In conclusion, we found that the incidence rate as well as prevalence of hospitalized gout increased in Denmark from 1995 to 2015 among both men and women. The reasons for this pattern are unclear but may include greater awareness of gout in the population and among health care providers as well as a greater impact of risk factors such as obesity, metabolic disorders and an ageing population. Further research is needed to elucidate the underlying causes of the observed increase in the incidence of gout.

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KZ, RC, PH has no competing interests.

KEYWORDS

Gout, Crystal Arthropathy, Epidemiology, Incidence, Prevalence.

KEY MESSAGES

“Rising epidemic of hospitalized gout in Denmark the previous 20 years.”

“The burden of hospitalised gouty arthritis is increasing for both sexes in Denmark.”

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